

REMARKS

The Examiner has objected to paragraph [0007] of the disclosure due to a lack of punctuation. As requested by the Examiner, the appropriate punctuation along with the conjunction "and" has been inserted. It is respectfully submitted that the language has been amended to overcome this objection. In addition, the Applicant has amended the bulleted number to be sequential.

Claims 1-2, 4-8, 10-23 and 25-35 remain in the Application. Applicant has deleted claims 3, 9, and 24 and has incorporated their limitations into parent claims. Applicant has amended Claims 1, 4, 8, 10, 15, 20, 23, 25, 27, 29 and 30, these amendments being fully supported by the application as originally filed. No new subject matter has been added.

Claim 15 has been amended to correct a typographical error.

Claim 20 has been amended to remove a period after "Cl, Br or I".

The Examiner has objected to claim 4 because it lacks suitable punctuation. As requested by the Examiner, the appropriate punctuation has been inserted. Again, it is respectfully submitted that the language has been amended to overcome this objection.

Claims 4-8, 11-23 and 26 are rejected under 35 U.S.C. 112, first paragraph. In particular, the Examiner states the specification is enable for a catalyst, such as palladium and nickel, cupric chloride, cupric bromide, cupric iodide, cuprous chloride, cuprous bromide, cuprous iodide, copper (I) oxide, copper (II) oxide or copper-zinc alloy and that the catalyst claims does not reasonably provide enablement for all the catalyst known in the chemical art. The Applicant has amended these claims by incorporating the limitations of deleted claims 9 and 24 into their parent independent claims 4 and 20 respectively. Thus claims 4-8, 11-23 and 26 now specify that the catalyst is a copper containing catalyst. Reconsideration is respectfully requested.

Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph. In particular, the Examiner states that the claims are incomplete for omitting essential steps, such omission amounting to a gap between the steps. The Applicant has amended these claims by specifying in Claim 1 that the ester of formula VII is made by reacting formula VI with a hydroxyl compound R^2OH . Furthermore, the

Applicant has incorporated the amide formation step of deleted Claim 3 into Claim 1 to specify how formula VI or VII forms flecainide. Reconsideration is respectfully requested.

Claims 8-10, 23-25 and 28-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

In particular, in claims 8 and 23, the Examiner has objected to the phrase "a base selected from potassium tert-butoxide, sodium tert-butoxide, sodium isopropoxide or sodium methoxide" is recited. The word "or" has been replaced with the word "and". Claims 8 and 23 have been amended to overcome Examiner's objection and full reconsideration is requested.

The Examiner has objected to claims 9, 10, 24 and 25 as the phrase "a copper type catalyst" and "the like" are recited. As discussed previously, the language of claims 9 and 24 have been incorporated into claims 4 and 20. The objectable language referred to by the Examiner has been replaced to specify that the catalyst is a copper containing catalyst which the Applicant believes is more acceptable and is fully supported by the disclosure, for example in paragraph [0014]. The term "and the like" has been deleted. In addition, the Applicant has amended Claim 10 to now depend on Claim 4 whereas it previously depended on Claim 9 which has now been deleted.

Claims 28-30 recite the limitation "(the) solvent(s)" in claim 27. The Examiner states that there is insufficient antecedent basis for this limitation in the claim. The Applicant respectfully disagrees with the objection to Claim 28 as Claim 28 is meant to introduce the further element that the reaction of claim 27 is carried out in solvents. Reconsideration is requested. Claims 29 and 30 which previously depended on Claim 27 have been amended, so that they now depend on Claim 28 which does provide sufficient antecedence for the term "solvents".

Claims 27-29, 31, and 33-34 are rejected under 25 U.S.C. 102(b) as being anticipated by Mcdaniel et al (WO 02/066413). The Applicant has amended these claims to specifically exclude any embodiments where the alkyl group is 2,2,2-trifluoroethyl or cyanomethyl groups. It is respectfully submitted that the rejection under 25 U.S.C. 102(b) has been traversed and reconsideration is respectfully submitted.

Claims 27-28 and 31 have also been rejected under 35 U.S.C. 102(b) as being anticipated by Banitt et al (US 4,005,209). As previously discussed, the Applicant has amended these claims to exclude embodiments where the alkyl group is 2,2,2-trifluoroethyl or cynomethyl groups. Reconsideration is requested.

The Examiner has also rejected under 35 U.S.C. 103(a) claims 27-34 as being obvious over Mcdaniel et al. in view of Banitt et al. The Applicant respectfully submits that the Examiner has not established a factually supported prima facie case for obviousness, as case law requires. Accordingly, the Applicant have no obligation to produce evidence of non-obviousness.

Establishment of a prima facie case of obviousness required three criteria:

- i. a suggestion or motivation, either in the prior art references themselves or in the knowledge generally available to the skilled artisan, to modify or combine the references;
- ii. a reasonable expectation of success; and
- iii. a teaching or suggestion of all of the claim limitations in the prior art reference or combination of references. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Moreover, under MPEP 2142, an Examiner is required to "step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. Knowledge of the applicants' disclosure must be put aside. ..."

Applicants submit that neither of the two documents relied upon by the Examiner for obviousness specifically teach the subject matter of currently amended claims 27-34, specifically the process using the structures of the compound wherein the alkyl group is anything other than 2,2,2-trifluoroethyl or for that matter, cynomethyl group. As a result, there is no suggestion or teaching of all of the claim limitations in the prior art. The Examiner has pointed to case law pointing out that "the substitution of methyl for hydrogen on known compound is not a patentable modification absent unexpected or unobvious results." The Applicant, however, respectfully disagrees with the examiner's citation and reliance on said case law. It is hopefully appreciated by the Examiner that both of the cases relied upon suggest that it would be obvious to substitute lower alkyl groups (like methyls) for hydrogens.

This is different from the present case as it would involve the substitution of 2,2,2-trifluoroethyl for other substituents.

In any event, even if this case law supports the notion that any other substituents could be substituted for the trifluoroethyl, which is denied, the Applicant states that there would be no reasonable expectation of success for the process as claimed in claims 27-34 by persons skilled in the art. The fact that the Applicant's have found that the reaction can work is an unexpected and unobvious result. As discussed in Applicant's disclosure, in paragraph [0005], it was previously thought that only the reactive trifluoroethyl and cyanomethyl esters could be used in the preparation of flecainide. The article *J. Med. Chem.*, 1977, 20, pp821-826, a copy of which is attached for Examiner's reference discloses at the bottom of page 821, right hand column that:

Trifluoroethylation of hydroxyl acids 1 by methods previously described gave the intermediate trifluoroethyl esters 2a. Usually these activated esters could be converted directly into benzamides, ... (Underline added)

The prior art thus taught that it was necessary to use activated or reactive esters in order to synthesize these types of compounds. There was no suggestion that the simple esters, which would not be considered to be reactive, as used in Applicant's claims would be expected to be useful or would be successful in completing the reaction.

This view is also further supported by *March's Advanced Organic Chemistry* p510, a copy of which is attached. This page specifically discloses that:

Many simple esters (R=Me, Et, etc.) are not very reactive, and strongly basic catalysis has been used, as well as catalysis by cyanide ion and high pressure.

Thus the person of ordinary skill in the art would have thought that only the use of strongly basic catalysis or catalysis using high pressure would result in a suitable reaction. Such a person would have no reasonable expectation that the use of simple esters as described in Applicant's claims would be successful. In light of the above argument and the newly submitted set of claims, the Applicant respectfully requests the Examiner to reconsider his rejection under 35 U.S.C. 103(a) on this point.

The Applicants respectfully submit that this application is now in condition for allowance, which action is earnestly solicited. If the Examiner has any questions, he is respectfully requested to contact Applicant's Agent, Francis Ng-Cheng-Hin at (905) 771-6414 collect at his convenience.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Francis Ng-Cheng-Hin', written in a cursive style.

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FN/md
Enclosures

1, H-1'). Anal. ($C_{18}H_{17}N_3O_6$) C, H, N.

References and Notes

- (1) R. A. Morton, Ed., "Biochemistry of Quinones", Academic Press, New York, N.Y., 1965.
- (2) O. Hoffmann-Ostenhof, *Metab. Inhibitors*, 2, 145 (1963).
- (3) V. Ambrogio et al., *Br. J. Pharmacol.*, 40, 871 (1970).
- (4) J. L. Webb, "Enzyme and Metabolic Inhibitors", Vol. 3, Academic Press, New York, N.Y., 1966, Chapter 5.
- (5) J. S. Driscoll, *Cancer Chemother. Rep., Part 2*, 4 (no. 4), 3 (1974); A. J. Lin, L. P. Cosby, and A. C. Sartorelli, *ibid.*, 4 (no. 4), 23 (1974).
- (6) J. S. Driscoll, G. F. Hazard, Jr., H. B. Wood, Jr., and A. Goldin, *Cancer Chemother. Rep., Part 2*, 4 (no. 2), 1 (1974).
- (7) M. F. Sartori, *Chem. Rev.*, 63, 279 (1963).
- (8) J. Skoda, *Prog. Nucleic Acid Res.*, 2, 214 (1963).
- (9) G. Alonso, G. Garcia-Muñoz, F. G. de las Heras, R. Madroño, and M. Stud, *J. Carbohydr., Nucleosides, Nucleotides*, 1, 381 (1974).
- (10) J. Doskočil, L. Kalvoda, and J. Krupička, *Biochem. Biophys. Res. Commun.*, 64, 932 (1975); L. Kalvoda, *Collect. Czech. Chem. Commun.*, 38, 1679 (1973).
- (11) U. Niedballa and H. Vorbrüggen, *Angew. Chem., Int. Ed. Engl.*, 9, 461 (1970).
- (12) J. R. E. Hoover and A. R. Day, *J. Am. Chem. Soc.*, 76, 4148 (1954).
- (13) L. F. Fieser and M. A. Peter, *J. Am. Chem. Soc.*, 53, 4080 (1931).
- (14) L. F. Fieser and E. L. Martin, *J. Am. Chem. Soc.*, 57, 1844 (1935).
- (15) G. R. Revankar and L. B. Townsend, *J. Heterocycl. Chem.*, 7, 1329 (1970); G. P. Kreishman, J. T. Witkowski, R. K. Robins, and M. P. Schweizer, *J. Am. Chem. Soc.*, 94, 5894 (1972); M. P. Schweizer, E. B. Banta, J. T. Witkowski, and R. K. Robins, *J. Am. Chem. Soc.*, 95, 3770 (1973).
- (16) M. Fuertes, R. K. Robins, and J. T. Witkowski, *J. Carbohydr., Nucleosides, Nucleotides*, 3, 169 (1976).
- (17) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, p 239.
- (18) J. L. Imbach, J. L. Barascut, B. L. Kam, B. Rayner, C. Tamby, and C. Tapiero, *J. Heterocycl. Chem.*, 10, 1069 (1973); J. L. Imbach, J. L. Barascut, B. L. Kam, and C. Tapiero, *Tetrahedron Lett.*, 129 (1974); J. L. Barascut, C. Tamby, and J. L. Imbach, *J. Carbohydr., Nucleosides, Nucleotides*, 1, 77 (1974).
- (19) F. F. Snyder, J. T. Henderson, and D. A. Cook, *Biochem. Pharmacol.*, 21, 2351 (1972).
- (20) H. Brockmann, K. Van Der Merwe, and A. Zeeck, *Chem. Ber.*, 97, 2555 (1964); H. Brockmann and T. Reschke, *Tetrahedron Lett.*, 4593 (1965).
- (21) R. W. Sidwell and J. H. Huffman, *Appl. Microbiol.*, 22, 797 (1971).

Antiarrhythmics. 2. Synthesis and Antiarrhythmic Activity of N-(Piperidylalkyl)trifluoroethoxybenzamides

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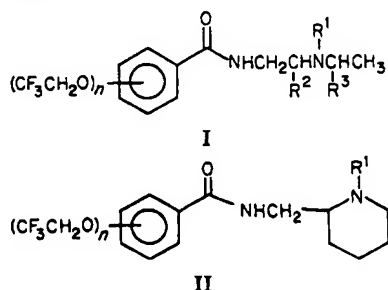
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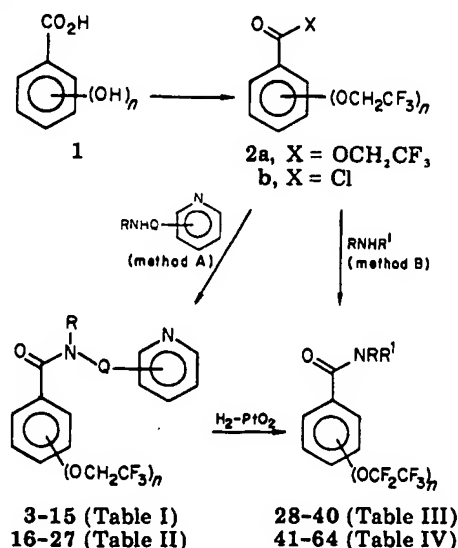
Benzamides characterized by one or more 2,2,2-trifluoroethoxy ring substituents and a heterocyclic amide side chain have been prepared and evaluated for oral antiarrhythmic activity in mice. The most potent compounds are derived from 2,5-bis(2,2,2-trifluoroethoxy)benzamide, and, within this group, both tertiary as well as secondary benzamides are active. Considerable variation in the heterocyclic ring is permissible, but antiarrhythmic activity is strongly influenced by the basicity of the amine nitrogen and the nature of the link between heterocycle and amide nitrogen. One of these compounds, N-(2-piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide acetate (flecainide acetate, USAN), was studied extensively in animals and selected for clinical trial as an antiarrhythmic.

In a previous paper¹ we described a series of N-(aminoalkyl)trifluoroethoxybenzamides which possessed potent antiarrhythmic properties. Within this series considerable variation of the amide side chain was possible without significant reduction in activity, but a structural feature common to a majority of the most potent compounds was an amide side chain with branching α to the basic nitrogen atom (I). We now wish to report a series of N-(piperidylalkyl)trifluoroethoxybenzamides, typified by the general structure II, which can be formally derived from I by linking R² and R³.

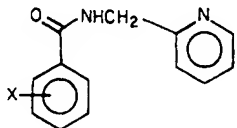


Chemistry. The trifluoroethoxybenzamides studied in

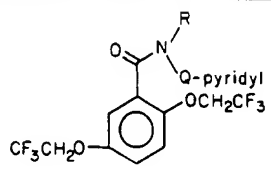
Scheme I



this investigation were prepared by the general routes outlined in Scheme I. Trifluoroethylation of hydroxy acids

Table I. Ring-Substituted *N*-(2-Pyridylmethyl)benzamide Intermediates


Compd	X	Mp, °C	Formula ^a	Recrystn solvent
3	2-OCH ₂ CF ₃	86-88	C ₁₅ H ₁₃ F ₃ N ₂ O ₂	Cyclohexane
4	3-OCH ₂ CF ₃	98-99	C ₁₅ H ₁₃ F ₃ N ₂ O ₂	EtOAc
5	4-OCH ₂ CF ₃	128-130.5	C ₁₅ H ₁₃ F ₃ N ₂ O ₂	EtOH-H ₂ O
6	2,3-(OCH ₂ CF ₃) ₂	144-146	C ₁₇ H ₁₄ F ₆ N ₂ O ₃	<i>i</i> -PrOH
7	2,4-(OCH ₂ CF ₃) ₂	103-105.5	C ₁₇ H ₁₄ F ₆ N ₂ O ₃	Cyclohexane-benzene
8	2,5-(OCH ₂ CF ₃) ₂	103-105	C ₁₇ H ₁₄ F ₆ N ₂ O ₃	Benzene-hexane
9	2,6-(OCH ₂ CF ₃) ₂	137-138.5	C ₁₇ H ₁₄ F ₆ N ₂ O ₃	Cyclohexane
10	3,4-(OCH ₂ CF ₃) ₂	117-118	C ₁₇ H ₁₄ F ₆ N ₂ O ₃	CCl ₄
11	3,5-(OCH ₂ CF ₃) ₂	103-104.5	C ₁₇ H ₁₄ F ₆ N ₂ O ₃	Toluene-heptane
12	2,4,6-(OCH ₂ CF ₃) ₃	155.5-157	C ₁₉ H ₁₅ F ₉ N ₂ O ₄	Cyclohexane-benzene
13	2-OCH ₂ CF ₃ , 5-CH ₃	99-100.5	C ₁₆ H ₁₅ F ₃ N ₂ O ₂	EtOH-H ₂ O
14	2-OCH ₂ CF ₃ , 5-Cl	119-121	C ₁₅ H ₁₂ ClF ₃ N ₂ O ₂	Cyclohexane-benzene
15	2-OCH ₂ CF ₃ , 5-F	114.5-116	C ₁₅ H ₁₂ F ₄ N ₂ O ₂	EtOH-H ₂ O

^a All compounds analyzed for C, H, and N within ±0.4% of the theoretical value.Table II. *N*-Substituted 2,5-Bis(2,2,2-trifluoroethoxy)benzamide Intermediates


Compd	R	Q-Pyridyl	Mp, °C	Formula ^a	Recrystn solvent
16	H	2-Pyridyl	166-179	C ₁₆ H ₁₂ F ₆ N ₂ O ₃ ·HCl	<i>i</i> -PrOH
17	H	3-Pyridyl	114-117	C ₁₆ H ₁₂ F ₆ N ₂ O ₃ ·0.5CCl ₄	<i>i</i> -PrOH-CCl ₄
18	H	4-Pyridyl	164.5-166.6	C ₁₆ H ₁₂ F ₆ N ₂ O ₃ ·HCl	EtOAc- <i>i</i> -PrOH
19	H	3-Pyridylmethyl	181-188	C ₁₇ H ₁₄ F ₆ N ₂ O ₃ ·HCl	<i>i</i> -PrOH
20	H	6-Methyl-3-pyridylmethyl	113-114.5	C ₁₈ H ₁₆ F ₆ N ₂ O ₃	CCl ₄ -cyclohexane
21	H	1-(2-Pyridyl)ethyl	98-100.5	C ₁₈ H ₁₆ F ₆ N ₂ O ₃	Cyclohexane
22	<i>n</i> -Bu	2-Pyridylmethyl	82-84	C ₂₁ H ₂₂ F ₆ N ₂ O ₃	Heptane
23	CH ₃	2-Pyridylmethyl	89-91	C ₁₈ H ₁₆ F ₆ N ₂ O ₃	Heptane-benzene
24	CH ₃	6-Methyl-3-pyridylmethyl	83-86	C ₁₉ H ₁₈ F ₆ N ₂ O ₃	Heptane-benzene
25	CH ₂ CH ₃	2-Pyridylmethyl	68-74	C ₁₉ H ₁₈ F ₆ N ₂ O ₃	Glass
26	C ₆ H ₁₁	2-Pyridylmethyl	113-114	C ₂₃ H ₂₄ F ₆ N ₂ O ₃	Cyclohexane
27	<i>t</i> -Bu	2-Pyridylmethyl	122-123.5	C ₂₁ H ₂₂ F ₆ N ₂ O ₃	Cyclohexane-hexane

^a See corresponding footnote in Table I.

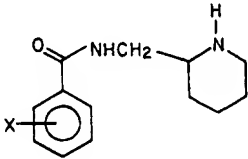
1 by methods previously described¹ gave the intermediate trifluoroethyl esters **2a**. Usually these activated esters could be converted directly into benzamides, but in certain cases it was necessary to use the corresponding acid chloride **2b**, obtained from **2a** by saponification followed by chlorination with thionyl chloride.

Most of the compounds were obtained from **2a** and **2b** in two steps (Scheme I, method A). Treatment of either intermediate with RNHQ-pyridine yielded a series of *N*-(Q-pyridyl)trifluoroethoxybenzamides (**3-27**, Tables I and II). In this scheme Q represents a methylene link, a substituted methylene link (**21**), or a carbon-nitrogen bond (**16-18**). With pyridines bearing a primary amine function (R = H), the method of choice was direct aminolysis of ester **2a** with excess amine. In cases where valuable amine had to be conserved, it was necessary to use acid chloride **2b**. The *tert-N*-alkyl-*N*-(Q-pyridyl)-trifluoroethoxybenzamides **22-27**, derived from pyridines with a bulky secondary amino group (R = alkyl), also required the use of **2b**. In either case, subsequent catalytic hydrogenation of the pyridine ring gave the desired piperidine compounds. The availability of required pyridines and lack of complications made the two-step synthesis a preferred route.

One-step conversion of **2a** and **2b** into *N*-(piperidylalkyl)trifluoroethoxybenzamides (method B) was achieved with certain fully saturated amine components RNHR¹ (R¹ = piperidyl or piperidylmethyl). With acid chloride **2b** this method is clearly limited to cases where no mixed products are possible, i.e., the ring nitrogen must be tertiary. In contrast, aminolysis of ester **2a** is highly selective and occurs preferentially with primary amines (R = H). Thus even if the ring nitrogen is secondary, aminolysis of **2a** with an excess of NH₂R¹ involves reaction at the exocyclic amine function only to give the desired products. All *N*-(piperidylalkyl)trifluoroethoxybenzamides (**28-64**) which were prepared by either method are collected in Tables III and IV.

Most of the amines required for the preparation of benzamides described in this paper are readily available. Exceptions include the 2-(alkylaminomethyl)pyridines which were used to synthesize benzamides **22-27**. These amines were obtained by condensing the appropriate primary amine with 2-pyridinecarboxaldehyde and hydrogenating the intermediate Schiff base without isolation according to a modification of the procedure described by Profft.² The isomeric diamines, 2-aminomethyl-1,2,3,4-tetrahydroquinoline and 1-aminomethyl-1,2,3,4-tetra-

Table III. Ring-Substituted N-(2-Piperidylmethyl)benzamides



Compd	X	Mp, °C	Formula ^a	Recrystn solvent	Synthetic method (yield, %)	Mouse protection screen, ED ₅₀ , μmol/kg po
Quinidine						217 (162-291) ^b
Procainamide						1030 (688-1545)
Lidocaine						495 (401-606)
28	2-OCH ₂ CF ₃	196-197.5	C ₁₅ H ₁₉ F ₃ N ₂ O ₃ ·HCl	<i>i</i> -PrOH	A (65) ^c	283 (212-394)
29	3-OCH ₂ CF ₃	107.5-109	C ₁₅ H ₁₉ F ₃ N ₂ O ₃	Cyclohexane	A (37)	76 (54-107)
30	4-OCH ₂ CF ₃	226-228	C ₁₅ H ₁₉ F ₃ N ₂ O ₃ ·HCl	<i>i</i> -PrOH-EtOH	A (47)	190 (128-278)
31	2,3-(OCH ₂ CF ₃) ₂	199-201	C ₁₇ H ₂₀ F ₆ N ₂ O ₃ ·HCl	<i>i</i> -PrOH-(<i>i</i> -Pr) ₂ O	A (80)	149 (111-202)
32	2,4-(OCH ₂ CF ₃) ₂	271-272	C ₁₇ H ₂₀ F ₆ N ₂ O ₃ ·HCl	MeOH	A (64)	244 (182-328)
33	2,5-(OCH ₂ CF ₃) ₂	145-147	C ₁₇ H ₂₀ F ₆ N ₂ O ₃ ·C ₂ H ₄ O ₂	<i>i</i> -PrOH-(<i>i</i> -Pr) ₂ O	A (76)	48 (36-65)
34	2,6-(OCH ₂ CF ₃) ₂	266-268	C ₁₇ H ₂₀ F ₆ N ₂ O ₃ ·HCl	EtOH	A (71)	271 (211-348)
35	3,4-(OCH ₂ CF ₃) ₂	157.5-159.5	C ₁₇ H ₂₀ F ₆ N ₂ O ₃ ·HCl	CH ₃ CN-(<i>i</i> -Pr) ₂ O	A (65)	277 (200-388)
36	3,5-(OCH ₂ CF ₃) ₂	202-204	C ₁₇ H ₂₀ F ₆ N ₂ O ₃ ·HCl	<i>i</i> -PrOH-(<i>i</i> -Pr) ₂ O	A (16)	388 (284-532)
37	2,4,6-(OCH ₂ CF ₃) ₃	264-265	C ₁₉ H ₂₁ F ₉ N ₂ O ₄ ·HCl	EtOH	A (74)	95 (73-124)
38	2-OCH ₂ CF ₃ , 5-CH ₃	193-196	C ₁₆ H ₂₁ F ₃ N ₂ O ₃ ·HCl	<i>i</i> -PrOH-(<i>i</i> -Pr) ₂ O	A (79)	> 600
39	2-OCH ₂ CF ₃ , 5-Cl	157-160	C ₁₅ H ₁₆ ClF ₃ N ₂ O ₃ ·HCl	<i>i</i> -PrOH-(<i>i</i> -Pr) ₂ O	A (82)	230 (173-287)
40	2-OCH ₂ CF ₃ , 5-F	200-201.5	C ₁₅ H ₁₆ F ₄ N ₂ O ₃ ·HCl	<i>i</i> -PrOH-(<i>i</i> -Pr) ₂ O	A (81)	270 (186-391)

^a All compounds analyzed for C, H, and N within ±0.4% of the theoretical value. ^b 95% confidence limits. ^c Yields listed for method A refer only to the final hydrogenation step.

hydroisoquinoline, were synthesized by the method of Rupe et al.³ and Katz and Popp,⁴ respectively.

Pharmacology. Prevention of chloroform-induced ventricular fibrillation in female mice (18-24 g) of Swiss-Webster origin was used for preliminary identification and quantification of antiarrhythmic activity.⁵ Control mice when exposed to chloroform vapors until cessation of respiration exhibit ventricular fibrillation upon visual inspection of the heart. Prevention of this response was taken as evidence of antiarrhythmic action. Sometimes after drug administration the response to subsequent chloroform exposure resulted in alternating periods of arrhythmia and/or fast ventricular rate (>200/min) with periods of normal rhythm and/or slow ventricular rate (<200/min). When this occurred, a predominance of normal rhythm and/or slow ventricular rate was taken as an indication of antiarrhythmic action. All test substances were administered orally using 4% acacia as a vehicle. Initially each test compound was given to a group of ten mice at a relatively high dose (range finding). Compounds which lacked potency compared to standard reference agents were disqualified from further testing. Compounds showing good activity at the initial dose were subsequently tested in groups of ten mice using 50% increments in dose as necessary to calculate ED₅₀ values according to the method of Litchfield and Wilcoxon.⁶ Results are expressed in Tables III and IV as ED₅₀ values (μmol/kg po) together with 95% confidence limits. The ED₅₀ values obtained in the same manner for the reference agents quinidine, procainamide, and lidocaine are included in Table III.

Discussion

Our earlier structure-action studies on N-(aminoalkyl)trifluoroethoxybenzamides¹ revealed that antiarrhythmic potency varied widely depending on the pattern of trifluoroethoxy ring substitution. Among N-(2-diethylaminoethyl)benzamides, the most potent activity was observed with compounds bearing two trifluoroethoxy groups, one of which was ortho to the carboxamide function. A similar trend was found in the present study although the variation in potency with substituent changes

was somewhat less pronounced.

The effect of ring substituent changes was evaluated with a set of N-(2-piperidylmethyl)benzamides (28-37, Table III). These compounds differ only in the number and position of trifluoroethoxy groups, and many have ED₅₀ values of 200-300 μmol/kg, putting them roughly in the same range as the reference agent quinidine in this test.

Among the monosubstituted compounds, a trifluoroethoxy group meta (29) to the carboxamide function is superior to substitution at either the ortho (28) or para (30) position. Of the six possible disubstituted isomers (31-36), four have at least one CF₃CH₂O group meta to the carboxamide. Two of the four, 31 [2,3-(OCH₂CF₃)₂; ED₅₀ = 149 μmol/kg] and 33 [2,5-(OCH₂CF₃)₂; ED₅₀ = 48 μmol/kg], are considerably more potent than the others. These are the only two isomers which have one CF₃CH₂O ortho and one CF₃CH₂O meta to the carboxamide function and this clearly represents the most favorable configuration. Replacement of the *m*-CF₃CH₂O in compound 33 with other substituents (38-40) results in substantial reduction in activity.

Since the best aromatic substitution pattern is unmistakably 2,5-(OCH₂CF₃)₂, all additional compounds designed to explore modification of the amide side chain were based on this ring nucleus. The various N-substituted 2,5-bis(2,2,2-trifluoroethoxy)benzamides 41-64 which were prepared and studied are collected in Table IV. Compounds 41-47 illustrate effects of altering the chain length between amide and amine nitrogen atoms. A two-carbon link between these sites is a common characteristic among many compounds with local anesthetic or antiarrhythmic activity.⁷ Although the amine nitrogen in the present series is part of a heterocyclic ring, a two-carbon link is still optimum whether the amide is bonded to a methylene (33, 41, 42) or directly to the ring (43). Extension of the chain to three (44, 45) or four carbons (46) results in marked reduction in activity, and this reduction is even more dramatic when the chain is shortened to one carbon atom (compare 33 and 47).

Most of the compounds reported here are secondary amines, but tertiary amines are also active. Thus 48

Table IV. N-Substituted 2,5-Bis(2,2,2-trifluoroethoxy)benzamides

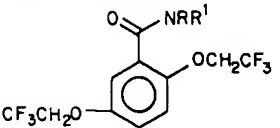
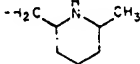




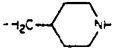


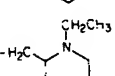
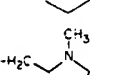
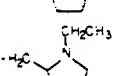
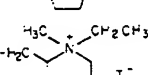
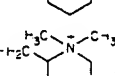

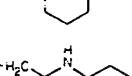
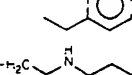



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Compd	R	R'	Mp or bp (mm), °C	Formula ^a	Recrystn solvent	Synthetic method (yield, %)	Mouse protection screen, ED ₅₀ , μmol/kg po	
41	H		215-222	C ₁₈ H ₂₂ F ₆ N ₂ O ₃ ·HCl	EtOH	A (46) ^b	22 (15-30) ^c	
42	H		95-97.5	C ₁₈ H ₂₂ F ₆ N ₂ O ₃	Cyclohexane	A (55)	19 (9-35)	
43	H		224-225	C ₁₆ H ₁₈ F ₆ N ₂ O ₃ ·HCl	EtOH- <i>i</i> -PrOH	A (18)	57 (39-82)	
44	H		189-191.5	C ₁₇ H ₂₀ F ₆ N ₂ O ₃ ·HCl	<i>i</i> -PrOH	A (65)	82 (58-118)	
45	H		193.5-195	C ₁₆ H ₁₈ F ₆ N ₂ O ₃ ·HCl	<i>i</i> -PrOH-(<i>i</i> -Pr) ₂ O	A (42)	144 (89-234)	
46	H		179-180	C ₁₇ H ₂₀ F ₆ N ₂ O ₃ ·HCl	EtOAc- <i>i</i> -PrOH	B (67)	149 (73-304)	
47	H		Glass	C ₁₆ H ₁₈ F ₆ N ₂ O ₃ ·HCl·0.75H ₂ O		A (88)	>500	
48	H		99-102	C ₁₈ H ₂₂ F ₆ N ₂ O ₃	Cyclohexane	C (61) ^d	44 (30-61)	
49	H		98-99	C ₁₉ H ₂₄ F ₆ N ₂ O ₃	Petr ether- cyclohexane	B (62)	102 (59-151)	
50	CH ₂ CH ₃		163 (0.2)	C ₁₉ H ₂₄ F ₆ N ₂ O ₃		A (80)	29 (20-43)	
51	H		78-80	C ₁₈ H ₂₂ F ₆ N ₂ O ₃	Petr ether- cyclohexane	B (59)	70 (47-105)	
52	H		162-165	C ₂₀ H ₂₆ F ₆ IN ₂ O ₃	MeOH-(<i>i</i> -Pr) ₂ O	D (76) ^d	>380	
53	H		170-172.5	C ₁₉ H ₂₃ F ₆ IN ₂ O ₃	EtOAc- <i>i</i> -PrOH	D (71)	>395	
54	H		90-94	C ₁₈ H ₂₀ F ₆ N ₂ O ₃	Benzene-hexane	E (58) ^d	>510	
55	H		196-206	C ₂₁ H ₂₆ F ₆ N ₂ O ₃ ·HCl	MeOH	B (48)	>450	
56	H		241-246	C ₂₁ H ₂₆ F ₆ N ₂ O ₃ ·HCl	CH ₃ CN-EtOH	B (24)	27 (14-53)	
57	H		103-109	C ₂₁ H ₂₆ F ₆ N ₂ O ₃	Cyclohexane	B (69)	380 (223-647)	
58	<i>n</i> -Bu		119-120	C ₂₁ H ₂₈ F ₆ N ₂ O ₃ ·C ₄ H ₉ O ₂	MIBK	A (49)	32 (25-40)	
59	CH ₃		113-115	C ₁₈ H ₂₂ F ₆ N ₂ O ₃ ·C ₄ H ₉ O ₂	MIBK- <i>i</i> -PrOH	A (81)	24 (20-27)	

Table IV (Continued)

Compd	R	R ¹	Mp or bp (mm), °C	Formula ^a	Recrystn solvent	Synthetic method (yield, %)	Mouse protection screen, ED ₅₀ , μmol/kg po
60	CH ₃		130-131	C ₁₉ H ₂₄ F ₆ N ₂ O ₃ ·C ₂ H ₄ O ₂	MIBK	A (72)	9 (7-12)
61	CH ₂ CH ₃		93-96	C ₁₉ H ₂₄ F ₆ N ₂ O ₃	Hexane	A (65)	<2
62	<i>n</i> -C ₆ H ₁₁		132-135	C ₂₃ H ₃₀ F ₆ N ₂ O ₃ ·0.86C ₄ H ₄ O ₄	EtOAc- <i>i</i> -PrOH	A (33)	36 (23-47)
63	<i>t</i> -Bu		110-112.5	C ₂₁ H ₂₈ F ₆ N ₂ O ₃	Cyclohexane-hexane	A (45)	17 (13-22)
64			101-105	C ₁₉ H ₂₂ F ₆ N ₂ O ₃	Cyclohexane-hexane	B (62)	>510

^a All compounds analyzed for C, H, and N within ±0.4% of the theoretical values. ^b Yields listed for method A refer only to the final hydrogenation step. ^c 95% confidence limits. ^d See Experimental Section.

(*N*-methyl) is comparable to 33 although 49 (*N*-ethyl) is less than one-half as potent. While no clear superiority can be demonstrated for either secondary or tertiary amines in the side chain, the need for an amino group of relatively strong basic strength is unmistakable. Thus quaternization (52, 53) or formylation (54) of the amine is unfavorable. Similarly compound 55, bearing a weakly basic arylamino group in the side chain, shows lower activity. The effect of basicity is dramatically illustrated by comparing 55 (ED₅₀ > 450 μmol/kg) with its saturated counterpart 56 (ED₅₀ = 27 μmol/kg). The presence of a six-membered heterocycle, however, is not essential since the two *N*-alkylpyrrolidines 50 and 51 show good activity.

As a class, the most active compounds in this entire series are the tertiary amides 50 and 58-63. All compare favorably with 33 in potency, but some also show increased toxicity (CNS depression). A curious exception to the general observation of excellent activity among tertiary amides is compound 64. The amide function in 64 is part of a rigid bicyclic ring system, and this structural alteration results in a significant reduction in activity.

The work reported here demonstrates that 2,5-bis-(2,2,2-trifluoroethoxy)benzamides bearing a piperidine ring as part of the amide side chain possess interesting and potent antiarrhythmic activity. Considerable latitude in the nature of the piperidine side chain is possible without loss of activity. On the basis of this preliminary work, several compounds were studied more extensively in canine model arrhythmias (e.g., ouabain-induced ectopic ventricular tachycardia and coronary ligation induced ventricular arrhythmia). One of these compounds, *N*-(2-piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide acetate (33; flecainide acetate, USAN), is currently being evaluated for antiarrhythmic activity in man. A short description of the pharmacological properties of 33 has already appeared,⁸ and a more detailed account will be published elsewhere.

Experimental Section

Boiling points are uncorrected. Melting points, determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus, are uncorrected. The general procedures outlined in Scheme I and listed in Tables III and IV are illustrated by the following examples.

Method A. *N*-(2-Pyridylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide (8). 2,2,2-Trifluoroethyl 2,5-bis(2,2,2-tri-

fluoroethoxy)benzoate¹ (21.6 g, 0.054 mol) was added neat over a period of 1 h to a stirred solution of 7.06 g (0.0648 mol) of 2-aminomethylpyridine in 100 mL of glyme under N₂ at 25 °C. The clear solution was stirred for 20 h at 25 °C and slowly brought to reflux. After 3 h the solution was cooled and concentrated in vacuo. Crystallization of the residue from benzene-hexane afforded 8 as an off-white solid: mp 103-105 °C; yield 20.1 g (91%).

***N*-(*n*-Butyl)-*N*-(2-pyridylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide (22).** A solution of 10.1 g (0.03 mol) of 2,5-bis(2,2,2-trifluoroethoxy)benzoyl chloride¹ in 30 mL of benzene was added dropwise at room temperature to a stirred suspension of 4.9 g (0.03 mol) of 2-(*n*-butylaminomethyl)pyridine, 13.7 g (0.12 mol) of Na₂CO₃, and 90 mL of benzene. After the addition was complete the mixture was heated under gentle reflux for 5 h, cooled, and concentrated under reduced pressure to remove benzene. Water and CH₂Cl₂ were added to the residue. The organic layer was separated, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Recrystallization of crude product from heptane gave 22 as white flakes: mp 82-84 °C; yield 10.5 g (75.5%).

***N*-(2-Piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide Acetate (33).** A solution of 40.8 g (0.01 mol) of compound 8 in 600 mL of HOAc was added under N₂ to a paste of 0.4 g of PtO₂ in HOAc and hydrogenated on a Parr apparatus. After the theoretical amount of H₂ had been taken up, the mixture was filtered to remove catalyst and the filtrate was refiltered with added Super Cel. Evaporation of the filtrate under vacuum left a viscous syrup which solidified on trituration with (*i*-Pr)₂O. The solid was collected by suction filtration and dissolved in hot *i*-PrOH. Crystallization was induced by adding (*i*-Pr)₂O to the cloud point. The purified product was collected as a white granular solid: mp 145-147 °C; yield 35.8 g (76%). This reduction can also be carried out in EtOH using a preformed HCl salt of the starting pyridylmethylbenzamide.

Method B. *N*-(4-Piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide Hydrochloride (46). 2,2,2-Trifluoroethyl 2,5-bis(2,2,2-trifluoroethoxy)benzoate (10.0 g, 0.025 mol) was added neat over a period of 1 h to a stirred solution of 28.5 g (0.25 mol) 4-aminomethylpiperidine in 25 mL of glyme. The mixture was stirred overnight at room temperature and poured into H₂O. Most of the glyme was removed by concentrating the aqueous mixture on a rotary evaporator. The solid which separated was collected by suction filtration, dried, and dissolved in EtOAc. 2-Propanolic HCl was added and the solution was cooled. The HCl salt was collected and recrystallized from EtOAc-*i*-PrOH: mp 179-180 °C; yield 7.4 g (67%).

Method C. *N*-(1-Methyl-2-piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide (48). 1-Methylpiperidine derivatives were prepared by the Eschweiler-Clarke reaction. Formalin (1.44 g, 0.048 mol), *N*-(2-piperidylmethyl)-2,5-bis-

(2,2,2-trifluoroethoxy)benzamide (8.3 g, 0.02 mol), and excess 88% formic acid (5.5 g, 0.12 mol) were combined and stirred under reflux. After 12 h the mixture was cooled and 2.8 mL of concentrated HCl was added. Heating under reflux was continued for another 5 h. The solution was then cooled, made strongly basic with 10% NaOH, diluted with H₂O, and extracted with CH₂Cl₂. Evaporation of solvent yielded 6 g of crude product which was purified by recrystallization from cyclohexane: mp 99–102 °C; yield 5.2 g (61%). Compounds of this type were also conveniently prepared by the Borch reductive amination procedure.⁹

Method D. 2-[2,5-Bis(2,2,2-trifluoroethoxy)benzamido-methyl]-1,1-dimethylpiperidinium Iodide (53). Compound 48 (2.7 g, 0.0063 mol) was heated with 10 mL of CH₃I in a sealed tube at 55 °C. After 1.5 h the tube was opened and the contents rinsed out with CH₃OH. Solvents were removed under vacuum and the residue was recrystallized from EtOAc-*i*-PrOH to give 53 as a white powder: mp 170–172.5 °C; yield 2.4 g (71%).

Method E. *N*-(1-Formyl-2-piperidylmethyl)-2,5-bis-(2,2,2-trifluoroethoxy)benzamide (54). Trichloroacetaldehyde (2.82 g, 0.019 mol) was added dropwise at 0 °C to a stirred solution of compound 33 (7.24 g, 0.0175 mol) in 70 mL of CHCl₃. After the addition was complete, the solution was allowed to warm to room temperature, stirred for 1 h, and then heated under reflux for 3 h. The solution was cooled, washed with 5% HCl, dried, and concentrated. The residual gummy solid was dissolved in hot benzene. Slow addition of hexane to the cloud point induced crystallization of 54 as a finely divided ivory powder: mp 90–94 °C; yield 4.6 g (58%).

2-(*tert*-Butylaminomethyl)pyridine. The general procedure used to prepare various 2-(alkylaminomethyl)pyridines is illustrated by the following example. A solution of 21.9 g (0.3 mol) of *tert*-butylamine in 30 mL of absolute EtOH was added dropwise over 1.5 h to a stirred solution of 32.1 g (0.3 mol) of 2-pyridine-

carboxaldehyde in 40 mL of absolute EtOH maintained at 10–20 °C. After the addition was complete, the mixture was stirred 1 h at 25 °C, heated to reflux for 6 h and cooled. GLC analysis showed that conversion to the Schiff base was essentially quantitative. The mixture was diluted with 150 mL of absolute EtOH and hydrogenated over 1 g of 10% Pd/C in a Parr apparatus. After removal of catalyst and solvent, the crude product was purified by distillation: bp 75–80 °C (1.2 mm); yield 40.4 g (82%). Purity was established by NMR and comparative GLC traces.

Acknowledgment. The authors wish to thank Mr. B. D. Seebeck for valuable technical assistance in performing the pharmacological evaluations.

References and Notes

- (1) E. H. Banitt, W. E. Coyne, J. R. Schmid, and A. Mendel, *J. Med. Chem.*, **18**, 1130 (1975).
- (2) E. Profft, *Chem. Tech. (Leipzig)*, **6**, 484 (1954).
- (3) H. Rupe, R. Paltzer, and K. Engel, *Helv. Chim. Acta*, **20**, 212 (1937).
- (4) L. E. Katz and F. D. Popp, *J. Heterocycl. Chem.*, **4**, 635 (1951).
- (5) J. W. Lawson, *J. Pharmacol. Exp. Ther.*, **160**, 22 (1968).
- (6) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).
- (7) J. Buchi and X. Perlia in "Drug Design", Vol. III, E. J. Ariens, Ed., Academic Press, New York, N.Y., 1972, p 241.
- (8) J. R. Schmid, B. D. Seebeck, C. L. Henrie, E. H. Banitt, and D. C. Kvam, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **34**, 775 (1975).
- (9) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).

Notes

Synthesis of 5-Chloro-3'-nitro-4'-substituted Salicylanilides, a New Series of Anthelmintic and Antimicrobial Agents¹

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A number of 5-chloro-3'-nitro-4'-substituted salicylanilides (6–23) have been synthesized by treating 4',5-dichloro-3'-nitrosalicylanilide (5) with various sodium aryl oxides, alkoxides, or amines. These compounds have been tested against *Hymenolepis nana* infection in rats and have also been evaluated for their in vitro antimicrobial activity against various strains of bacteria and fungi. In the former test 17 was the most active cestocidal agent showing activity at 30 mg/kg. In the antimicrobial screening, 22 inhibited the growth of all the bacteria and fungi used while 6 was active against the penicillin resistant *Staphylococcus aureus* at a minimum inhibitory concentration of 0.00609 µg/mL.

It has been observed that introduction of a phenoxy group in a biologically active molecule may lead to compounds with enhanced activity.^{2,3} One example is the discovery of 3'-chloro-4'-(*p*-chlorophenoxy)-3,5-diiodo-salicylanilide (rafoxanide, 1).⁴ Based on this observation, the synthesis of various 5-chloro-3'-nitro-4'-aryloxy-salicylanilides (6–9), as the structural analogues of the well-known cestocidal, 2,5'-dichloro-4'-nitrosalicylanilide (2),⁵ has been carried out. Unlike 2, in which ring B is substituted by two electron-withdrawing groups (Cl and

NO₂) at the 2 and 4 positions, respectively, the compounds reported in this communication carry one electron-withdrawing NO₂ group at the 3 position and one electron-donating aryloxy group in the 4 position of ring B. Compounds 10–23 with other electron-donating groups like ethoxy, dialkylamino, and cyclic imino have also been prepared for structure-activity relationship studies. These compounds have been tested for their in vivo cestocidal activity. In addition, they have also been subjected to in vitro antimicrobial screening and the results are reported

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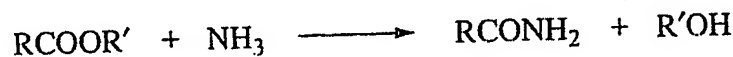
(such as DHU), side products, and the solvents themselves are quickly washed away. Purification of the polymeric species (such as **104**, **105**, and **106**) is rapid and complete. The process can even be automated,¹⁰²⁹ to the extent that six or more amino acids can be added to a peptide chain in 1 day. Commercial automated peptide synthesizers are now available.¹⁰³⁰

Although the solid-phase technique was first developed for the synthesis of peptide chains and has seen considerable use for this purpose, it has also been used to synthesize chains of polysaccharides and polynucleotides; in the latter case, solid-phase synthesis has almost completely replaced synthesis in solution.¹⁰³¹ The technique has been applied less often to reactions in which only two molecules are brought together (nonrepetitive syntheses), but many examples have been reported.¹⁰³²

OS I, 3, 82, 111, 172, 327; II, 65, 562; III, 95, 328, 475, 590, 646, 656, 768; IV, 6, 62, 513; V, 670, 1070; VIII, 241. Also see OS III, 360; VI, 263; VIII, 68.

10-58 Acylation of Amines by Carboxylic Esters

AMINO-DE-ALKOXYLATION



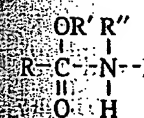
The conversion of carboxylic esters to amides is a useful reaction, and unsubstituted, N-substituted, and N,N-disubstituted amides can be prepared this way from the appropriate amine.¹⁰³³ Both R and R' can be alkyl or aryl. An especially good leaving group is *p*-nitrophenyl. Ethyl trifluoroacetate was found to react selectively with primary amines to form the corresponding trifluoroacetyl amide.¹⁰³⁴ Many simple esters (R = Me, Et, etc.) are not very reactive, and strongly basic catalysis has been used,¹⁰³⁵ as well as catalysis by cyanide ion¹⁰³⁶ and high pressure.¹⁰³⁷ Lithium amides have been used to convert esters to amides as well.¹⁰³⁸ β -Keto esters undergo the reaction especially easily.¹⁰³⁹ In another procedure, esters are treated with dimethylaluminum amides ($\text{Me}_2\text{AlNRR}'$) to give good yields of amides under mild conditions.¹⁰⁴⁰ The reagents are easily prepared from Me_3Al and NH_3 or a primary or secondary amine or their salts. This is particularly effective when a reactive substituent, such as a primary halide, is present elsewhere in the molecule.¹⁰⁴¹ Tin reagents such as $\text{Sn}[\text{N}(\text{TMS})_2]_2$ in the presence of an amine can also be used to convert an ester to an amide.¹⁰⁴² This reagent can also be used to convert β -amino esters to β -lactams.¹⁰⁴³ The ester-to-amide conversion has also been accomplished electrochemically, by passing electric current in the cathodic compartment.¹⁰⁴⁴

As in 10-55 hydrazides and hydroxamic acids can be prepared from carboxylic esters, with hydrazine and hydroxylamine, respectively. Both hydrazine and hydroxylamine react more rapidly than ammonia or primary amines (the α effect, p. 445). Imidates, $\text{RC}(=\text{NH})\text{OR}'$, give amidines, $\text{RC}(=\text{NH})\text{NH}_2$. Lactones, when treated with ammonia or primary amines, give lactams. Lactams are also produced from γ - and δ -amino esters in an internal example of this reaction.

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